CORRESPONDENCE

New SARS-CoV-2 Variants — Clinical, Public Health, and Vaccine Implications

TO THE EDITOR: Across the world, there are multiple variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19). SARS-CoV-2 variants have been classified by the Centers for Disease Control and Prevention (CDC) as variants of interest, variants of concern, and variants of high consequence. Three new variants[1] that have rapidly become dominant within their countries have aroused concerns: B.1.1.7 (also known as VOC-202012/01), 501Y.V2 (B.1.351), and P.1 (B.1.1.28.1).

The B.1.1.7 variant (23 mutations with 17 amino acid changes) was first described in the United Kingdom on December 14, 2020; the 501Y.V2 variant (23 mutations with 17 amino acid changes) was initially reported in South Africa on December 18, 2020; and the P.1 variant (approximately 35 mutations with 17 amino acid changes) was reported in Brazil on January 12, 2021. By February 22, 2021, the B.1.1.7 variant had been reported in 93 countries, the 501Y.V2 variant in 45, and the P.1 variant in 21.[1] All three variants have the N501Y mutation, which changes the amino acid asparagine (N) to tyrosine (Y) at position 501 in the receptor-binding domain of the spike protein. The 501Y.V2 and P.1 variants both have two additional receptor-binding–domain mutations, K417N/T and E484K. These mutations increase the binding affinity of the receptor-binding domain to the angiotensin-converting enzyme 2 (ACE2) receptor. Four key concerns stemming from the emergence of the new variants are their effects on viral transmissibility, disease severity, reinfection rates (i.e., escape from natural immunity), and vaccine effectiveness (i.e., escape from vaccine-induced immunity).

The 501Y.V2 variant spread rapidly in South Africa, accounting for 11% of the viruses sequenced (44 of 392) in the first week of October 2020, for 60% of those sequenced (302 of 505) in the first week of November 2020, and for 87% of those sequenced (363 of 415) in the first week of December 2020. In Western Cape, a South African province where the 501Y.V2 variant is predominant, a threshold of 100,000 cases of Covid-19 was reached approximately 50% more quickly in the second wave of infection than in the first wave (54 vs. 107 days). The 501Y.V2 variant has been estimated to be 50%[2] more transmissible than preexisting variants in South Africa, and B.1.1.7 to be between 43% and 82%[3] more transmissible than preexisting variants in the United Kingdom.

Hospital admission rates of diagnosed cases and the clinical profile of admitted patients were similar in the first and second waves in Western Cape. However, a preliminary analysis by the National Institute of Communicable Diseases showed that the 501Y.V2 variant was associated with in-hospital mortality that was 20% higher in the second wave in South Africa than in the first wave. This finding was due mainly to the greater transmissibility of this variant, which rapidly overburdened health services and thus compromised timely access to hospital care and the quality of that care. Evidence from the United Kingdom indicates that the B.1.1.7 variant may be associated with a higher risk of death than preexisting variants in the United Kingdom.[4] Although there is no evidence that antiviral agents and antiinflammatory treatments are any less effective with the emerging variants than with the preexisting variants, treatment with convalescent serum and monoclonal antibodies may not be as effective.

With regard to escape from natural immunity, the B.1.1.7 variant showed a modest decrease in neutralization activity, by a factor of 1.5, whereas the 501Y.V2 variant showed complete escape from neutralizing antibodies in 48% of convalescent serum samples (21 of 44) obtained from patients who had previously had Covid-19.[5] A serendipitous finding from a vaccine trial in South Africa, in which 31% of the enrolled participants had previously been infected with SARS-

Table 1. Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, as Compared with Preexisting Variants.*

Vaccine (Company)	Preexisting Variants			Neutralization by Pseudovirion or Live Viral Plaque Assay			Efficacy in Settings with 501Y.V2 Variant
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19	B.1.1.7 Variant	P.1 Variant	501Y.V2 Variant	
	no.	*% (no. of events with vaccine vs. placebo)*					%
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)	NA	NA	NA	57†, 85‡
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)	Decrease by 2×	Decrease by 6.7×	Decrease by ≤6.5×	NA
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)	Decrease by 1.8×	Decrease by 4.5×	Decrease by ≤8.6×	NA
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)	NA	NA	NA	NA
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)	NA	NA	Decrease by ≤86× to complete immune escape	22§
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)	Decrease by 1.8×	NA	NA	49§
CoronaVac (Sinovac)¶							
Brazil	12,396	51 (NA)	100 (NA)	NA	NA	NA	NA
Turkey	7,371	91 (3 vs. 26)	NA	NA	NA	NA	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA	NA	NA	Decrease by 1.6×	NA

* Data were available up to March 18, 2021. The definitions of mild, moderate, and severe coronavirus disease 2019 (Covid-19) vary across the vaccine trials. A list of references associated with these vaccines is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. NA denotes not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Shown is the efficacy of the vaccine, as compared with placebo, against moderate-to-severe Covid-19.
‡ Shown is efficacy of the vaccine, as compared with placebo, against severe Covid-19 and hospitalization.
§ Shown is efficacy of the vaccine, as compared with placebo, against symptomatic Covid-19.
¶ Data are shown separately for the trial sites in Brazil and Turkey.

CoV-2, was that the incidence of Covid-19, as confirmed on polymerase chain reaction, was 7.9% among seronegative enrollees and 4.4% among seropositive enrollees in the placebo group. This finding indicates that previous infection with preexisting variants may provide only partial protection from reinfection with the 501Y.V2 variant.

With regard to escape from vaccine-induced immunity, the B.1.1.7 variant showed modest decreases in neutralizing activity in serum samples obtained from vaccinated persons (Table 1). The serum neutralizing activity for the 501Y.V2 variant among vaccinated persons was lower by a factor of 1.6 to 8.6 for the BBIBP-CorV vaccine, the BNT162b2 vaccine, and the mRNA-1273 vaccine but was lower by a factor of up to 86, including complete immune escape, for the AZD1222 vaccine (Table 1). Neutralizing activity for the P.1 variant among vaccinated persons was lower by a factor of 6.7 for the BNT162b2 vaccine and by a factor of 4.5 for the mRNA-1273 vaccine (Table 1). The clinical relevance of the lower neutralization activity for either mild or severe Covid-19 is not clear, but efficacy in clinical trials was lower for all three vaccines tested in the midst of transmission of the 501Y.V2 variant in South Africa than efficacy in trials conducted in countries with preexisting variants. Efficacy was higher by a factor of 3.2 with the AZD1222 vaccine in the United Kingdom and Brazil than in South Africa (70% vs. 22%), higher by a factor of 1.8 with the NVX-CoV237 vaccine in the United Kingdom than in South Africa (89% vs. 49%), and higher by a factor of 1.3 with the Ad26.COV2.S vaccine in the United States than in South Africa (72% vs. 57%).

The emergence of these three new variants of concern highlight the importance of vigilance with genomic surveillance for the early identification of future variants. Recently, two more SARS-CoV-2 variants, B.1.427 and B.1.429, which were first detected in California, have been shown to be approximately 20% more transmissible than preexisting variants and have been classified by the CDC as variants of concern. The potential of variants to escape naturally induced and vaccine-induced immunity makes the development of next-generation vaccines that elicit broadly neutralizing activity against current and potential future variants a priority. The suppression of viral replication with both public health measures and the equitable distribution of vaccines is critical in reducing the risk of generation of new variants.

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